WHAT IS CLAIMED IS:

1. A variant of a parent polypeptide comprising an Fc region, which variant mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of human effector cells more effectively, or binds an Fc gamma receptor (FcγR) with better affinity, than the parent polypeptide and comprises at least one amino acid modification in the Fc region.

2. The variant of claim 1 which comprises an antibody.

3. The variant of claim 1 wherein the parent polypeptide Fc region comprises a human IgG Fc region.

4. The variant of claim 3 wherein the human IgG Fc region comprises a human IgG1, IgG2, IgG3 or IgG4 Fc region.

5. The variant of claim 1 which mediates ADCC about 1.5 fold to about 100 fold more effectively than the parent polypeptide.

6. The variant of claim 1 which binds an FcγRIII with better affinity than the parent polypeptide.

7. The variant of claim 6 which further binds an FcγRII with worse affinity than the parent polypeptide.

8. The variant of claim 1 which comprises at least one amino acid substitution in the Fc region.

9. The variant of claim 1 which comprises at least one amino acid modification in a CH2 domain of the Fc region.

10. The variant of claim 1 which comprises at least one amino acid modification in the Fc region, other than in a lower hinge region thereof.

= claims 1–10 of
[illegible]

11. The variant of claim 1 which comprises an amino acid substitution at any one or more of amino acid positions 256, 290, 298, 312, 326, 330, 333, 334, 360, 378 or 430 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

12. The variant of claim 11 which comprises two or more amino acid substitutions at the amino acid positions listed therein.

13. The variant of claim 11 which comprises three or more amino acid substitutions at the amino acid positions listed therein.

14. A polypeptide comprising a variant Fc region with altered Fc gamma receptor (FcγR) binding affinity, which polypeptide comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438 or 439 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

15. The polypeptide of claim 14 wherein the variant Fc region comprises a variant human IgG Fc region.

16. The polypeptide of claim 14 which displays reduced binding to an FcγR and comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

17. The polypeptide of claim 14 which displays reduced binding to an FcγRI.

18. The polypeptide of claim 17 which displays reduced binding to the FcγRI and comprises an amino acid modification at any one or more of amino acid 238, 265, 269, 270, 327 or 329 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

19. The polypeptide of claim 14 which displays reduced binding to an FcγRII.

20. The polypeptide of claim 19 which displays reduced binding to the FcγRII and comprises an amino acid modification at any one or more of amino acid positions 238, 265, 269, 270, 292, 294, 295, 298, 303, 324, 327, 329, 333, 335, 338, 373, 376, 414, 416, 419, 435, 438 or 439 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

21. The polypeptide of claim 14 which displays reduced binding to an FcγRIII.

22. The polypeptide of claim 21 which displays reduced binding to the FcγRIII and comprises an amino acid modification at any one or more of amino acid 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 293, 294, 295, 296, 301, 303, 322, 327, 329, 338, 340, 373, 376, 382, 388, 389, 416, 434, 435 or 437 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

23. The polypeptide of claim 14 which displays increased binding to an FcγR and comprises an amino acid modification at any one or more of amino acid positions 255, 256, 258, 267, 268, 272, 276, 280, 283, 285, 286, 290, 298, 301, 305, 307, 309, 312, 315, 320, 322, 326, 330, 331, 333, 334, 337, 340, 360, 378, 398 or 430 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

24. The polypeptide of claim 23 which displays increased binding to an FcγRIII.

25. The polypeptide of claim 24 which further displays decreased binding to an FcγRII.

26. The polypeptide of claim 25 which displays increased binding to the FcγRIII and further displays decreased binding to the FcγRII, wherein the polypeptide comprises an amino acid modification at positions 298 and/or 333 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

27. The polypeptide of claim 23 which displays increased binding to an FcγRII.

28. The polypeptide of claim 27 which displays increased binding to the FcγRII and comprises an amino acid modification at any one or more of amino acid 255, 256, 258, 267, 268,

272, 276, 280, 283, 285, 286, 290, 301, 305, 307, 309, 312, 315, 320, 322, 326, 330, 331, 337, 340, 378, 398 or 430 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

29. The polypeptide of claim 27 which further displays decreased binding to an FcγRIII.

30. The polypeptide of claim 29 which displays increased binding to the FcγRII and further displays decreased binding to the FcγRIII, wherein the polypeptide comprises an amino acid modification at any one or more of amino acid positions 268, 272, 298, 301, 322 or 340 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

31. A polypeptide comprising a variant Fc region with altered neonatal Fc receptor (FcRn) binding affinity, which polypeptide comprises an amino acid modification at any one or more of amino acid positions 238, 252, 253, 254, 255, 256, 265, 272, 286, 288, 303, 305, 307, 309, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 386, 388, 400, 413, 415, 424, 433, 434, 435, 436, 439 or 447 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

32. The polypeptide of claim 31 which displays reduced binding to an FcRn.

33. The polypeptide of claim 32 which displays reduced binding to the FcRn and comprises an amino acid modification at any one or more of amino acid positions 252, 253, 254, 255, 288, 309, 386, 388, 400, 415, 433, 435, 436, 439 or 447 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

34. The polypeptide of claim 31 which displays increased binding to FcRn.

35. The polypeptide of claim 34 which displays increased binding to FcRn and comprises an amino acid modification at any one or more of amino acid positions 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

= claims 29-35 of 463,527

36. The polypeptide of claim 14 which displays reduced binding to FcγRI, FcγRIIA, FcγRIIB and FcγRIIIA and comprises an amino acid modification at any one or more of amino acid positions 238, 265, 327 or 329 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

37. The polypeptide of claim 14 which displays reduced binding to FcγRII and FcγRIIIA and comprises an amino acid modification at any one or more of amino acid positions 270, 295 or 327 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

38. The polypeptide of claim 14 which displays increased binding to FcγRII and FcγRIIIA and comprises an amino acid modification at any one or more of amino acid positions 256 or 290 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

39. The polypeptide of claim 14 which displays increased binding to FcγRII but unchanged binding to FcγRIIIA and comprises an amino acid modification at any one or more of amino acid positions 255, 258, 267, 272, 276, 280, 285, 286, 307, 309, 315, 326, 331, 337, 378 or 430 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

40. The polypeptide of claim 14 which displays increased binding to FcγRII and reduced binding to FcγRIIIA and comprises an amino acid modification at any one or more of amino acid positions 268, 301 or 322 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

41. The polypeptide of claim 14 which displays reduced binding to FcγRII but unchanged FcγRIIIA binding and comprises an amino acid modification at any one or more of amino acid positions 292 or 414 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

42. The polypeptide of claim 14 which displays reduced binding to FcγRII and improved binding to FcγRIIIA and comprises an amino acid modification at amino acid position 298 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

43. The polypeptide of claim 14 which displays reduced binding to FcγRIIIA but unchanged FcRII binding and comprises an amino acid modification at any one or more of amino acid positions 239, 269, 293, 296, 303, 327, 338 or 376 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

44. The polypeptide of claim 14 which displays improved binding to FcγRIIIA but unchanged FcRII binding and comprises an amino acid modification at any one or more of amino acid positions 333 or 334 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

45. The polypeptide of claim 31 which displays altered binding to FcRn but unchanged FcγR binding and comprises an amino acid modification at any one or more of amino acid positions 253, 254, 288, 305, 311, 312, 317, 360, 362, 380, 382, 415, 424, 433, 434, 435 or 436 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

46. The polypeptide of claim 1 which comprises an amino acid modification at any one or more of amino acid positions 298, 333 or 334 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

47. The polypeptide of claim 1 which comprises amino acid modifications at two or more of amino acid positions 298, 333, 334 or 339 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

48. The polypeptide of claim 46 which comprises an amino acid modification at amino acid position 298 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

49. The polypeptide of claim 46 which comprises amino acid modifications at amino acid positions 298 and 334 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

50. The polypeptide of claim 46 which comprises amino acid modifications at three or more of amino acid positions 298, 333, 334 or 339 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

51. The polypeptide of claim 46 which comprises amino acid modifications at amino acid positions 298, 333 and 334 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

52. The polypeptide of claim 1 which further displays increased binding to neonatal Fc receptor (FcRn).

53. The polypeptide of claim 33 which comprises an amino acid modification at one or more of amino acid positions 253, 254, 435 or 436 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

54. The polypeptide of claim 35 which comprises an amino acid modification at one or more of amino acid positions 238, 256, 307, 311, 312, 380, 382 or 434 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

55. The polypeptide of claim 54 which comprises amino acid modifications at two or all of amino acid positions 307, 380 and 434 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

56. The polypeptide of claim 55 which comprises amino acid modifications at amino acid positions 307, 380 and 434 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

57. A polypeptide comprising a variant Fc region which comprises amino acid modifications at amino acid positions 298, 333 and 334 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

58. A polypeptide comprising a variant Fc region which comprises amino acid modifications at amino acid positions 298 and 334 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

59. A polypeptide comprising a variant Fc region which comprises an amino acid modification at amino acid position 298 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

60. A polypeptide comprising a variant Fc region with altered affinity for an $Fc\gamma R$ allotype, which polypeptide comprises an amino acid modification at any one or more of amino acid positions 265, 267, 268, 270, 290, 298, 305, 307, 315, 317, 320, 331, 333 or 334 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

61. The polypeptide of claim 60 wherein the $Fc\gamma RIII$ allotype is selected from the group consisting of $Fc\gamma RIIIA$-Phe158, $Fc\gamma RIIIA$-Val158, $Fc\gamma RIIA$-R131 and $Fc\gamma RIIA$-H131.

62. The polypeptide of claim 60 which displays increased binding to $Fc\gamma RIIIA$-Phe158.

63. The polypeptide of claim 62 comprising an amino acid modification at any one or more of amino acid positions 290, 298, 333 or 334 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

64. A polypeptide comprising a variant Fc region which comprises amino acid modifications at two or all of amino acid positions 307, 380 and 434 of the Fc region, wherein the numbering of the residues is that of the EU index as in Kabat.

65. The polypeptide of claim 64 which comprises amino acid modifications at amino acid positions 307, 380 and 434 of the Fc region, wherein the numbering of the residues is that of the EU index as in Kabat.

66. A composition comprising the polypeptide variant of claim 1 and a pharmaceutically acceptable carrier.

67. The composition of claim 66 which is sterile.

68. Isolated nucleic acid encoding the polypeptide variant of claim 1.

69. A vector comprising the nucleic acid of claim 68.

70. A host cell containing the vector of claim 69.

71. A method for producing a polypeptide variant comprising culturing the host cell of claim 70 so that the nucleic acid is expressed.

72. The process of claim 71 further comprising recovering the polypeptide variant from the host cell culture.

73. A method for treating a disorder in a mammal comprising administering to the mammal a therapeutically effective amount of the polypeptide variant of claim 1.

74. A method for making a variant Fc region with altered Fc receptor (FcR) binding affinity, or altered antibody-dependent cell-mediated cytotoxicity (ADCC) activity, comprising:

(a) introducing one or more amino acid modifications into an Fc region of a parent polypeptide in order to generate a variant Fc region;

(b) determining binding of the variant Fc region to an FcR, or determining ADCC activity of the variant Fc region.

75. The method of claim 74 wherein step (b) comprises determining binding of the variant Fc region to an FcR *in vitro.*

76. The method of claim 74 wherein step (b) comprises identifying a variant Fc region with improved FcR binding affinity, or with improved ADCC activity.

77. The method of claim 74 wherein the FcR is human Fc gamma receptor III ($Fc\gamma RIII$).

78. The method of claim 74 wherein step (b) comprises determining binding of the variant Fc region to at least two different FcRs.

79. The method of claim 79 wherein the Fc receptors include human Fc gamma receptor II ($Fc\gamma RII$) and human Fc gamma receptor III ($Fc\gamma RIII$).

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